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Acute cardioversion vs a wait-and-see approach for recent-onset symptomatic atrial fibrillation in the emergency department: Rationale and design of the randomized ACWAS trial

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Background Current standard of care for patients with recent-onset atrial fibrillation (AF) in the emergency department aims at urgent restoration of sinus rhythm, although paroxysmal AF is a condition that resolves spontaneously within 24 hours in more than 70% of the cases. A wait-and-see approach with rate-control medication only and when needed cardioversion within 48 hours of onset of symptoms is hypothesized to be noninferior, safe, and cost-effective as compared with current standard of care and to lead to a higher quality of life.

Design The ACWAS trial (NCT02248753) is an investigator-initiated, randomized, controlled, 2-arm noninferiority trial that compares a wait-and-see approach to the standard of care. Consenting adults with recent-onset symptomatic AF in the emergency department without urgent need for cardioversion are eligible for participation. A total of 437 patients will be randomized to either standard care (pharmacologic or electrical cardioversion) or the wait-and-see approach, consisting of symptom reduction through rate control medication until spontaneous conversion is achieved, with the possibility of cardioversion within 48 hours after onset of symptoms. Primary end point is the presence of sinus rhythm on 12-lead electrocardiogram at 4 weeks; main secondary outcomes are adverse events, total medical and societal costs, quality of life, and cost-effectiveness for 1 year.

Conclusions The ACWAS trial aims at providing evidence for the use of a wait-and-see approach for patients with recent-onset symptomatic AF in the emergency department. (Am Heart J 2017;183:49-53.)

Background and hypothesis

Recent-onset atrial fibrillation (AF) is one of the most common arrhythmias seen in the emergency department (ED). Current standard of care for patients with symptomatic AF in the ED, according to ESC guidelines, is mainly aimed at urgent restoration of sinus rhythm (ie, cardioversion).[1] This is usually achieved by pharmacologic cardioversion (PCV), electrical cardioversion, or a combination of both.

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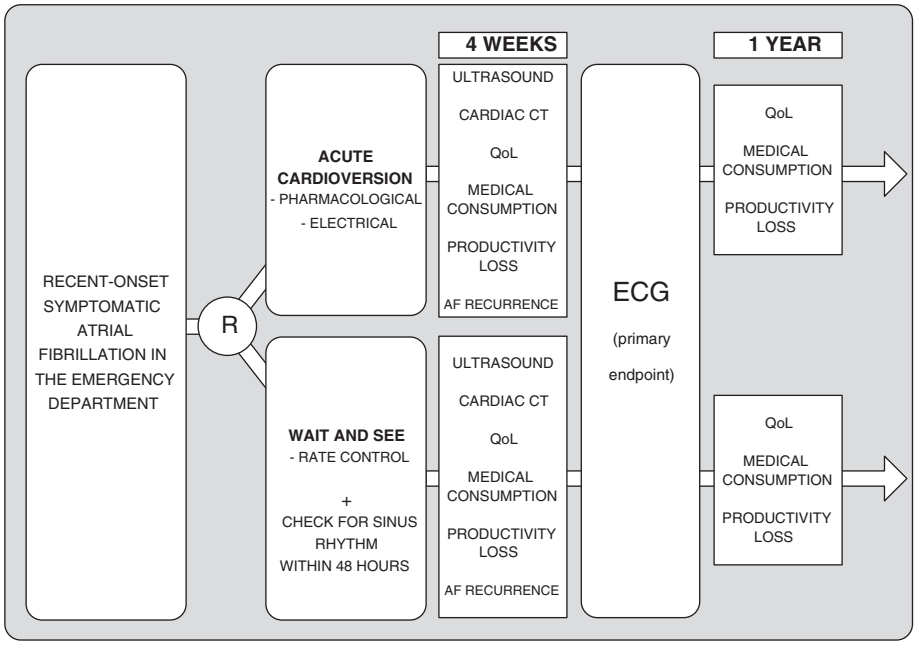
Figure 1



Flowchart of the study design of the ACWAS trial. R, randomization; CT, computed tomography.

Although immediate cardioversion of patients is proven to be effective in acute restoration of sinus rhythm,[2-4] one could question the need for immediate restoration of sinus rhythm because AF is a condition that resolves spontaneously within 24 hours in more than 70% of the cases.[5-7] In addition, it is known that the symptoms of AF can successfully be alleviated through medication that lowers the heart rate (rate control medication, such as β-blockers, calcium antagonists, or digoxin).[8] In the long term, there is no difference in prognosis between restoration of sinus rhythm (rhythm control) and rate control strategies.[9,10] Lastly, early cardioversion disallows the physician to critically observe the electroechocardiographic atrial substrate for the arrhythmia,[11] the possibility to achieve adequate rate control, and the natural course of the AF episode, including spontaneous conversion.

Considering the above, acute cardioversion can be seen as a form of overtreatment with respect to long-term restoration of sinus rhythm, and it may not necessarily influence development of cardiovascular and cerebrovascular events. Furthermore, avoiding cardioversion could lower costs and prevent procedure-related adverse effects. This study aims to prove that a wait-and-see approach (symptom alleviation and delayed cardioversion when necessary) is safe and noninferior on the presence of sinus rhythm at 4 weeks, when compared with standard of care (immediate cardioversion), while leading to lower health care costs and potentially a higher quality of life (QoL).

Trial oversight

The ACWAS trial is an investigator-initiated, multicenter, randomized, prospective 2-arm trial with either acute cardioversion or a wait-and-see approach for patients with recent-onset symptomatic AF at the ED. Thirteen cardiology departments (3 academic and 10 peripheral) will be participating in this trial. The study was approved by the institutional review board of the Maastricht Academic Hospital/Maastricht University, the Netherlands. The statistical analyses will be performed by the investigators together with an independent statistician who is involved in the preparation, analysis, evaluation, and presentation of the study data. The ACWAS trial is registered at ClinicalTrials.gov (NCT02248753) and the Netherlands Trial Register (NTR4663). A trial oversight is presented in Figure 1.

Patient selection

All patients at the ED with recent-onset (<36 hours) AF without signs of myocardial ischemia and hemodynamic instability are eligible to participate. Patients must be suitable for both acute cardioversion and the wait-and-see approach (Table I).

Blood sampling

Upon signing of informed consent, additional blood will be drawn and stored at −80°C for genetic analysis and

Table I. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
• ECG with AF at the ED	• Signs of myocardial infarction on ECG
	• Hemodynamic instability
	o (systolic blood pressure < 100 mm Hg, heart rate > 170 beats/min)
	• Presence of ventricular preexcitation syndrome/accessory conduction pathway
	• History of sick sinus syndrome
• Heart rate > 70 beats/min	• History of unexplained syncope
• Symptoms most probable due to AF	• History of persistent AF
• Duration of symptoms <36 h	• Acute heart failure
• Age >18 y	• Deemed unsuitable for participation by attending physician
• Able and willing to sign informed consent	• Previously enrolled in the ACWAS trial
• Able and willing to use MyDiagnostick	• Currently enrolled in another clinical trial

future biomarker analysis for biochemical phenotyping of the atrial substrate and the correlation with the duration of the AF attack, and for building prediction models for spontaneous conversion.

Randomization

Patients will be randomized in a 1:1 fashion to either acute cardioversion or wait-and-see approach. Randomization will be stratified per center, age, sex, and first or recurrent paroxysm. Randomization group will not be blinded to attending physician and patient.

Acute cardioversion

Pharmacologic cardioversion

In the acute cardioversion group, first choice of treatment is immediate PCV through intravenous flecainide (2 mg/kg body weight (150 mg maximum) in 10 minutes). Infusion will be halted in case of conversion to sinus rhythm, QRS widening (>50%) or adverse effects (ventricular arrhythmia, atrial flutter with 1: 1 conduction, hypotension or acute heart failure, AV block, or allergic reaction).

Electrical cardioversion

In case of contraindications, previous failure of PCV or current failure of PCV, electrical cardioversion will be performed under full sedation. A maximum of 3 shocks will be delivered from a biphasic defibrillator in synchronized mode via self-adhesive electrode pads in the anterior-apex scheme. Energy will be set at 200, 360, and 360 J.

Clinically stable patients will be discharged from the hospital after short (telemetric) observation. Patients will be admitted in case of complications during or after cardioversion, that is, ventricular arrhythmia, hemodynamic instability, or underlying sinus node dysfunction.

Wait-and-see approach

Patients in the intervention group will be discharged from the hospital upon cessation of symptoms through sufficient rate control (heart rate < 100 beats/min). Rate control is achieved through the use of intravenous metoprolol (bolus of 5 mg intravenous, repeated up to 3 times with 5 minutes in between), intravenous verapamil (5-10 mg in 2 minutes, repeated up to 3 times with 15 minutes in between) or, in case of contraindications for both, intravenous digoxin (0.5-1 mg). Upon discharge, the drug is continued orally. Patients will be asked to carry a Holter device to register exact time of conversion until the visit to the outpatient clinic or ED, which is planned as close as possible to 48 hours after onset of symptoms, yet allowing enough time to perform cardioversion within 48 hours after onset of symptoms. This ensures that a paroxysm will always terminate within 48 hours. During this visit, a 12-lead electrocardiogram (ECG) will be recorded. In case of continuing presence of AF, cardioversion as described above will be attempted.

Anticoagulation and medication at discharge

All patients will receive CHA_2DS_2-VASc–guided anticoagulation therapy as indicated by current guidelines.[1,12] First-time AF patients will be initiated on oral anticoagulant therapy during the index visit. The paroxysm of AF in both arms of the study will always terminate within 48 hours, either spontaneously or by cardioversion, which is within the safety margin for anticoagulation-naïve patients.

Upon discharge, in patients in both arms, the need to initiate or intensify oral rate or rhythm control drugs will be evaluated.

Follow-up

Upon conversion to sinus rhythm, patients in both groups will be asked to use a MyDiagnostick, 3 times daily

or whenever symptomatic, to determine heart rhythm, until the next outpatient visit at 4 weeks after the index visit. This validated device will be used to monitor (time to) recurrence of AF, and, in that case, AF burden.[13]

In case of recurrent AF paroxysm during follow-up, either detected by the MyDiagnostick or through patient symptoms, patients will be treated according to the treatment group to which they have been randomized. Patients in the intervention group will be treated according to the results of the rate control treatment during the index visit: in case of early spontaneous conversion using rate control drugs only, extra rate control medication is to be taken at home. Patients in the control group, or patients who failed to convert spontaneously, will undergo acute cardioversion. All patients can contact or visit the ED at any time.

Except for treatment in case of a recurrent paroxysm, treatment will not deviate from the current standard of care according to local protocols and is not influenced by study protocol. Patients will be scheduled for a computed tomographic angiogram and cardiac ultrasound, if standard of care according to local hospital protocols. All patients will visit a cardiologist at the outpatient clinic after 4 weeks, where a 12-lead ECG will be recorded. The presence of sinus rhythm on this ECG is the primary outcome measure. Atrial fibrillation–related complaints will be recorded and standard physical examination will be performed. The treating cardiologist will initiate or continue standard treatment of AF, which will not be specified by study protocols.

Patients will be asked to fill out questionnaires at 4 time points: baseline and 1, 6, and 12 months after inclusion, either through Internet survey or via mail. At each time point, QoL will be measured through Atrial Fibrillation Effect on QualiTy-of-Life[14] and 36-item Short-Form Health Survey[15] questionnaires. Furthermore, at each time point, medical consumption of patients inside and outside the hospital will be registered using the iMTA Medical Cost Questionnaire,[16] whereas productivity loss will be measured using the iMTA Productivity Cost Questionnaire.[17]. Medical files will be assessed for all medical events, including major adverse cardiac and cerebrovascular events, medication use, and the use of attempts to achieve rhythm control. The patient's general practitioner will be contacted to check for visits to other hospitals. Associated documents will be requested.

Statistical analysis

Primary end point and sample size calculation

The primary end point is the presence of sinus rhythm on the ECG at 4 weeks after the index visit. This is based on the pathophysiological principle that AF begets AF,[18] from which it may be concluded that not terminating a paroxysm of AF may lead to progression toward more frequent and longer paroxysms, potentially leading to persistent AF. It is thus chosen as a safety end point, to ensure that the wait-and-see approach does not lead to higher rates of AF progression. There is no reason to assume that there would be a difference in rates of adverse events between the 2 groups.

Sinus rhythm on the ECG at 4 weeks after the index visit is expected to be present in 90% of the patients in the control group.[15] A noninferiority margin of 10% is considered acceptable, given the natural variation in the presence of sinus rhythm, the generally low impact of the absence of sinus rhythm on the well-being of the patient, and the availability of good treatment options should treatment be necessary.

With a significance level (α) of .05, a power of 80%, proportion of 0.9 in the control group, and 0.8 in the intervention group, and relative sample size of 1.0, 437 patients are required to detect a difference between the treatment groups (continuity correction applied).[16]

Interim analysis

The institutional review board judged this study to be a low-risk trial; hence, we did not install a data safety monitoring board. However, we decided to plan an interim analysis at 4 weeks after the inclusion of the 219th patient (primary end point available in half of the patients). An independent Interim Analysis Commission, in which an independent statistician and a cardiologist not involved in the execution of this trial will take place, will evaluate the interim results of the trial. First, because of the uncertainty about the actual outcome rate, they will assess whether the trial is underpowered or overpowered on the primary end point. To this end, the Interim Analysis Commission will receive the percentage of patients in sinus rhythm for the total study population, not stratified per randomization arm. Based on this percentage, the sample size will be recalculated. In a second phase, they will evaluate the safety of continuing the trial, by assessing whether the percentage of patients in sinus rhythm in the experimental group is >10% lower than in the control group, or a significant difference in adverse event rate between the treatment arms is found.

Primary analysis

The difference between the groups in the proportion of patients in sinus rhythm and its 95% CI will be calculated using the exact method.

Additional analyses

All patient baseline continuous variables will be expressed as mean ± SD and categorical variables as percentage values. The primary outcome measure (presence of sinus rhythm at 4 weeks) will be presented as number (percentage) of patients. Time-to-recurrence, number of recurrences, and number of complications and adverse events will be displayed quantitatively. Differences between normally distributed continuous variables will be tested with an independent t test. Differences between variables with no normal distribution

will be tested with the Mann-Whitney *U* test. Categorical variables will be tested with Fisher exact test or χ^2 test. Statistical significance is accepted at the 95% CI ($P < .05$).

A univariate analysis of the factors that may influence the spontaneous termination of AF (including age, gender, cardiovascular history, risk factors, and biomarkers) will be performed. All covariates showing a univariate relation ($P < .1$) with spontaneous termination will be included in a logistic regression model.

Economic evaluation

The economic evaluation will be performed from both health care and societal perspective (productivity loss or out-of-pocket costs). To address the question regarding cost-effectiveness, both a cost-effectiveness analysis and cost-utility analysis from a societal perspective will be performed.

For the cost-effectiveness analysis, the primary clinical outcome, sinus rhythm at 4 weeks, will be used. The incremental costs per quality-adjusted life year will be calculated using results from the QoL questionnaires (Atrial Fibrillation Effect on QualiTy-of-Life[13] and 36-item Short-Form Health Survey[14]). The friction cost method will be used to calculate the productivity costs according to Dutch guidelines.[19] For the comparison of resource use, differences between the 2 groups will be analyzed with bias-corrected bootstrap analysis, as most volumes of resource use follow a skewed distribution. In addition, bootstrap analysis will also be used to quantify the uncertainty surrounding the incremental cost-effectiveness ratio. Results of this analysis will be presented in cost-effectiveness planes and acceptability curves. According to the International Society for Pharmacoeconomics and Outcomes Research task force principles, budget impact analysis will be performed next to the economic evaluation.

Conclusion

Summary

The ACWAS study will provide results that can guide the treatment of recent-onset symptomatic AF in the ED. It will show whether a wait-and-see approach compared with acute cardioversion is noninferior, safe, and cost-effective. In that case, the wait-and-see approach would be a worthy alternative to acute cardioversion.

Disclosures

Conflicts of interest: None. All authors have approved the final article.

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